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Prolonged febrile seizures: neuroanatomical and functional consequences

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Rationale and Objectives

Febrile seizures are common, affecting 2–5% of infants and young children worldwide (1–3). The relationship of childhood febrile seizures to adult temporal lobe epilepsy (TLE) has remained a focus of intense controversy (see 4–7 for brief recent reviews): Whereas prospective epidemiological studies have not shown a progression of febrile seizures to TLE, retrospective analyses of adults with TLE have demonstrated a high prevalence (30-$>$60%) of a history of *prolonged* (longer than 10–15 minutes) febrile seizures during early childhood, suggesting an etiological role for these seizures in the development of TLE. Specifically, neuronal damage induced by febrile seizures has been suggested as a mechanism for the development of mesial temporal sclerosis, the pathological hallmark of TLE. However, this high correlation should not be taken to indicate a causal relationship, and alternative mechanisms may exist for the correlation of prolonged febrile seizures and TLE. These involve pre-existing, genetic or acquired, functional or structural neuronal changes, that may underlie both the prolonged febrile seizures and the subsequent TLE (see diagram):

Alternative I:

Normal brain → Febrile seizures → neuronal damage → TLE

Alternative II:

Pre-existing injury/lesion → fever-triggered seizure = first sign of TLE

These critical questions regarding the causal relationship of prolonged febrile seizures and TLE are difficult to resolve in human studies. However, animal models permit induction of febrile seizures of controlled duration, and prospective studies for dissecting out the nature of these seizures and their consequences. Therefore, a model of febrile seizures in the immature rat, using animals during a brain-development age generally equivalent to that of the human infant and young child, has been developed and characterized (8). This model has been used to determine the acute and long-term consequences of prolonged hyperthermic seizures on neuronal function and survival both *in vivo* and *in vitro*, and on the development of spontaneous limbic seizures- i.e., TLE. Hyperthermic seizures, provoked by generating brain- temperatures seen physiologically in ill infants and children, were shown to result in structural alterations of select hippocampal and amygdala neurons (9). These changes in cellular cytoskeleton, leading to affinity of neurons to silver stains (argyrophilia) were not induced by hyperthermia alone: they were not found in animals subjected to the same magnitude and duration of hyperthermia, but in whom seizures were prevented by a short-acting barbiturate. The same study showed that although neurons in hippocampus and amygdala, in a distribution consistent with the injury found in TLE, were altered for at least 2 weeks, neuronal death was negligible. First, a time-course of *in situ* end labeling, performed 1, 4, 8.5, 20 or 48 hours after the seizures, did not reveal appreciable numbers of dying neurons. In addition, cell counts in highly involved limbic regions were similar in animals one month after prolonged hyperthermic seizures, hyperthermia alone or control conditions (9).

However, several key questions remained. First, are the apparently transient alterations of neuronal structure induced by hyperthermic seizures associated with functional disruption sufficient to alter the excitation-inhibition balance in the involved circuits, promoting the development of TLE? Second, are there other, more subtle neuroanatomical/structural alterations of hippocampal neurons, short of overt death, that may influence the hippocampal circuit to promote excitability?

Methods and Results

Addressing the first question, Chen et al. (10), demonstrated the presence of persistent functional modulation of hippocampal circuitry in this immature rat model of febrile seizures. Specifically, hyperthermia-induced seizures (but not hyperthermia alone) caused a selective presynaptic increase of inhibitory synaptic transmission in hippocampus, that lasted into adulthood. This paper thus documented, using controlled, prospective methods, that in a previously normal immature brain, experimental prolonged febrile seizures *caused long-lasting modifications of the balance of excitation and inhibition in neuronal microcircuits within the limbic system*. The changes found, however, seemed to imply increased activity of inhibitory interneurons, and the relationship between these alterations of synaptic communication and the development of limbic epilepsy was not resolved. In addition, these dramatic changes were shown *in vitro*, and their relevance to the whole organism required further study.

The consequences of prolonged febrile seizures in the immature rat model on the development of spontaneous seizures were the focus of a second study (7). Using *in vivo* and *in vitro* approaches in this model, it was determined that prolonged hyperthermia-induced seizures in immature rat caused long-term enhanced susceptibility to limbic convulsants that lasted to adulthood. After induction of prolonged (20 minutes) hyperthermic seizures, animals were allowed to grow to adulthood, then underwent extensive hippocampal EEGs and behavioral monitoring. Both EEGs and behavioral measures failed to demonstrate spontaneous seizures in these adult rats who had experienced hyperthermic seizures during infancy. However, 100% of animals developed hippocampal seizures upon systemic administration of a threshold dose of kainic acid, an activator of a glutamate receptor subtype. Thus, whereas this dose of the excitatory trigger did not cause seizures in most adult rats that did not experience prolonged febrile seizures in "infancy", i.e., both normothermic controls and those undergoing hyperthermia with seizure blockade, the majority of adult animals who had experienced prolonged febrile seizures early in life progressed to status epilepticus (SE). These findings, of a profound increase in vulnerability to pro-convulsant provocation, were confirmed *in vitro:* Spontaneous epileptiform discharges were not observed in hippocampal-entorhinal cortex slices derived from either control or experimental groups. However, Schaeffer collateral stimulation induced prolonged, self-sustaining, SE-like discharges exclusively in slices from experimental rats. These data indicate that hyperthermic seizures in the immature rat model of prolonged febrile seizures do not cause spontaneous limbic seizures during adulthood. However, they reduce thresholds to chemical convulsants *in vivo* and electrical

stimulation *in vitro*, indicating persistent enhancement of limbic excitability that may facilitate the development of epilepsy.

What are the underlying mechanisms for this profound and persistent enhancement of hippocampal excitability? In the absence of overt loss of hippocampal principal cells, functional changes in key components of the hippocampal circuit are under investigation. The possibility of subtle loss of discrete, vulnerable neuronal populations is being examined; recruitment of newly born neurons and re-wiring of dentate gyrus circuitry (e.g., granule cell axonal "sprouting") after febrile seizures are being considered. In addition, modulation of programs of gene expression in specific neuronal subtypes, that should govern their functional properties, are being pursued, to provide a better understanding of the molecular-cellular mechanisms by which prolonged febrile seizures in the immature rat model may promote a seizure-prone state.

Conclusion

Prolonged febrile seizures in the immature rat model modulate hippocampal excitability long-term. The molecular and electrophysiological mechanisms underlying this enhanced excitability may be unique- and thus amenable to therapeutic targeting. The precise mechanisms and consequences of these seizures, and the implication of these new data for the human situation require further investigations.

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